REMARKS/ARGUMENTS

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of three months of the period for response to the Office Action. The Commissioner is hereby authorized to charge the prescribed fee as indicated in the fee transmittal form.

The Examiner indicates that the attempt to incorporate subject matter into this application by reference to US application No. 08/923,558 is improper because the method of immunizing the mice is considered essential practise of the invention. Example 3 does not compare results of this application and those of US 08/923,558.

All the essential information and results obtained are contained in Example 3. The protocol of immunization is identified. The control group was immunized with 2 x 25 μg of SFV-RSV F RNA, which is described in US Patent No. 6,060,308, except that the muscles were not pretreated with cardiotoxin. The immunization protocol is set forth in Table 1.

The processing of the sera and the results obtained and disclosed in Example 3. It is not clear in what respect the Examiner considers Example 3 to be incomplete. It is submitted that no modification is required to the specification in this respect.

The Examiner has requested that the status of the US application referred to in the disclosure be updated. As known to the Examiner, for some reason which is by no reasons apparent, the pagenation of the version of the specification filed in this application and that in applicants file is different, leading to difficulties in identifying modifications to be made to the specification.

The following is a list of the patent applications referred to in the specification and their status. It is requested that the Examiner modify the disclosure by Examiner's amendment.

Application	Status
07/773,949	US Patent No. 6,245,549
08/476,397	US Patent No. 6,019,980
08/896,500	US Patent No. 6,017,897
08/923,558	US Patent No. 6,060,308

09/190,245 Now abandoned.

The Examiner considered the addition of the ATCC deposition 203461 to be new matter. The deposit date has been changed to the received date of November 12, 1998, as indicated by the Examiner.

As to evidence that the inventors deposited 203461 so that the deposit will be maintained according to the Budapest Treaty, this objection is not understood. The deposit form previously provided clearly identifies the deposit as being under the Budapest Treaty.

No affidavit or declaration of the time informed to by the Examiner. Under the heading "Biological Deposits" on pages 21 and 22, these are the following statements.

> "Certain vectors that contain the gene encoding RSV F protein and referred to herein have been deposited with the American Type Culture Collection (ATCC) located at 10801 University Boulevard, Manassas, VA 20110-2209, U.S.A., pursuant to the Budapest Treaty."
>
> ".... all restrictions on access to the deposits will be irrevocably removed at that time."
>
> "non-viable deposits will be replaced."

Deposit Summary

Plasmid	ATCC Designation	Date Deposited
pMP37	97905	Feb. 27, 1997
pMP42	203441	November 12, 1998

The specification thus specifically clearly states:

- pMP37 and pMP42 were deposited at the ATCC
- the name and address of the depository
- the restrictions on access will be removed upon grant
- non-viable deposits will be replaced

It is submitted that all requirements with respect to deposits have been met.

The Examiner rejected claims 1, 6, 8 to 10, 14 to 19 and 36 to 38 under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that

the inventor(s), at the time the application was filed, had possession of the described invention.

The Examiner indicates that the specification does not provide a written description for any fragment of F or G proteins of RSV that induce production of antibodies, as claimed. The Examiner asserts that the specification does not provide a written description of fragment of RSV F or G protein lacking the transmembrane anchor and cytoplasmic tail. The Examiner further asserts that such fragments were not known in the art at the time of filing.

First of all, the applicants refer to such fragments at a number of locations in the specification. Second, such fragments were known in the art and are described, for example, in US Patent No. 6,017,897 and its corresponding cited Li et al WO 96/40945 and US Patent Nos. 6,171,783 and 6,225,091 and their corresponding WO 93/14207 It is further noted that, to simplify the language of claim 1, the references to fragments that induce antibodies has been deleted.

Having regard thereto, it is submitted that claims 1, 6, 8 to 10, 14 to 19 and 36 to 38, insofar as they remain in the application and in their amended form, fully comply with the provision of 35 USC 112, first paragraph, in this regard.

The Examiner rejected claims 1, 6, 8 to 10, 14 to 19 and 36 to 38 under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in relevant art that the inventors, at the time the application was filed had possession of the claimed invention.

The Examiner raised a number of issues. However, the Examiner characterized amended claim 1 as "new matter". New matter is not a ground of rejection under 35 USC 112, first paragraph:

- The Examiner asserted that the specification does not teach a truncated RSV F or G protein that lacks the transmembrane anchor and cytoplasmic tail or that induce production of antibodies as desired. In this regard, the Examiner's attention is directed to the remarks above concerning written description of these features. This feature is found in original claim 7.

- The Examiner indicates that the specification does not teach that the second sequence is downstream of the first. In this regard, claim 1 has been amended to recited the original language, reciting the second sequence is inserted into a region of the first DNA sequence which is non-essential to replication.
- The Examiner indicates that the specification does not teach that the third DNA sequence is between the first DNA sequence and the promoter. A cursory examination of the drawings, for example, Figure 2B, will reveal the location. The specific location of the third sequence is also referred to at several locations in the specification. The specific location was referred to in original claim 13.
- The Examiner indicates that the specification does not teach that the third sequence has a pair of splice sites that prevent aberrant RNA splicing *in vivo*. This feature was recited in original claim 12. This feature also is clearly described in the specification and is illustrated in the drawings.

As noted earlier, the Examiner indicates that claim 1 as amended is new matter. Since features added to claim 1 were originally found in subclaims, these can be no new matter. Having regard to the above and the changes made to claim 1, it is submitted that claims 1, 6, 8 to 10, 14 to 19 and 36 to 38, insofar as they remain in the application and in their amended form, fully comply with the provisions of 35 USC 112, first paragraph, in this respect.

The Examiner rejected claims 1, 6, 8 to 10, 14 to 19 and 36 to 38 under 35 USC 112, first paragraph, because the specification, while enabling for immunogenic compositions, does not reasonably provide enablement for enhancing the immunoprotective ability of the paramyxovirus when expressed *in vivo* from the vector in a host. The Examiner considers that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention commensurate in scope with these claims.

The only claims directed to a immunogenic composition, namely claims 36 to 38, have been deleted. The remaining claims refer to a vector and not to an

immunogenic composition. It is not clear, therefore, why the Examiner is referring to claim 1 in a rejection of non-enablement of an immunogenic composition.

With respect to the Examiner's specified comments:

- RSV F or G fragments have been discussed above two times already and the Examiner's attention is directed thereto.
- The first, second and third sequences are already shown to be under the control of a single promoter in Figure 2B.
- The same figure clearly shown the third sequence between the first DNA sequence and the promoter.
- The specification clearly describes that the second sequence has a pair splice sites which prevent aberrant mRNA splicing in vivo.
- The specification clearly describes how to construct the vector. In this regard, reference is made to Examples 1 and 2 and Figures 1 and 2.

Having regard thereto, it is submitted that claims 1, 6, 8 to 10, 14 to 19 and 36 to 38, insofar as they remain in the application and in their amended form, are fully enabled and comply with the provisions of 37 CFR 112, first paragraph.

The Examiner rejected claims 1, 6, 8 to 10, 14 to 19 and 36 to 38 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point to and distinctly claim the subject matter which applicants regards as the invention

The Examiner considered claim 1 to be indefinite on the basis that it does not clearly set forth the structure or function of the DNA sequences in the vector.

The Examiner considered the first DNA sequence to be indefinite on the basis that it is unclear how "complementary" the DNA sequence is to the RNA genome. The term "complementary" or "complement" always refers to something which is the complementary according to the genetic code of the DNA/RNA sequences referred to. Claim 1 has been amended to refer to the sequence being wholly complementary to the alphavirus genome.

The Examiner considered that it is unclear whether the phrase "and having the complement of complete alphavirus RNA genome replication" refers to the first DNA sequence or the RNA genome. The conjunctive word "and" specifically

recites that the first DNA sequence has the complement of complete alphavirus RNA genome replication regions. Having regard to the Examiner's comment, claim 1 has been further amended to specifically recite that the first DNA sequence has the recited RNA genome replication genome.

With respect to the comment that the phrase "the complement" lacks antecedent basis, every DNA/RNA sequence has a complement according to the genetic code and it is in this context that the claims refer to "the complement". No antecedent language is required.

The Examiner asserts that it is unclear what applicants consider to be the complete alphavirus RNA genome replication regions that provide *in vivo* replication. The Examiner asserts that replication regions that provide *in vivo* replication are not defined in the specification or at the time of filing. In this regard, the Examiner's attention is directed to WO 95/27044, referred in the specification and published well before the filing of this application.

Accordingly, the structure and function of the first DNA sequence is not indefinite.

The Examiner considered the second DNA sequence to be indefinite on the basis that the species of the Markush group are not clearly set forth. In particular, the Examiner indicates that it is unclear if the "fragment" is a RSV F or G fragment or any fragment that induces production of antibodies that are specific with the RSV protein. The Examiner suggests that the term "and" should be used "before the last species of the group".

First of all, reference to a fragment that induces production of antibodies that specifically react with the RSV protein has been deleted from claim 1. In any event, it was clear from the language that the fragments used are the recited truncated RSV F or G protein lacking the transmembrane anchor and cytoplasmic tail.

Further, the Markush group is the RSV protein ("selected from the group consisting of the F and G glycoprotein of RSV"). The term "or" qualifies an alternative encoded RSV protein. The Markush group does not include the truncated RSV F or G protein.

Accordingly, th structure and function of the second DNA sequence is not indefinite.

The Examiner considered the third DNA sequence to be indefinite on the basis that the phrase "said third DNA sequence enhancing the immunoprotective ability of the RSV protein". While the phrase is quite clear in scope, it has been deleted from claim 1.

With respect to the remaining matters raised with respect to the third DNA sequence:

- the term "the RSV protein or fragment thereof" no longer appears in claim 1.
- the term "the immunoprotective ability" no longer appears in claim 1.
- the term "the promoter sequence" has been amended to read "the promoter"
- the term "and comprising a pair of splice sites that prevents aberrant mRNA splicing *in vivo*" has been amended to read "said third DNA sequence comprising a pair of splice sites that prevent aberrant splicing *in vivo*". Aberrant splicing is a phenomenon well known in the art.

Accordingly, it is submitted that the definition of the third DNA sequence is clear in scope.

The Examiner considered that the entire alphavirus sequence of the "first DNA sequence" and the splice sites of the "third DNA sequence" are not under control of the same promoter or the "second DNA sequence". It is unclear what basis the Examiner makes the assertion. The three sequences is clearly shown under control of the same promoter in Figures 2B.

The Examiner indicates that the location of the splice sites in pMP44 cannot be determined. Figure 2B shows pMP44. The splice sites are provided by the sequence encoding the rabbit ß-globin intron II, which is clearly labelled in Figure 2B.

With respect to the Examiner's concerns with respect to the subclaims:

- claim 6 recites that the second DNA sequence encodes a full-length RSV F or G protein, i.e. one of the options recited in claim 1. Claim 7 recites the other option, namely the truncated protein.
- claim 8 is quite clear. Claim 1 recites an alphavirus while claim 8 identifies a specific alphavirus, namely Semliki forest virus.
- claim 9 is clear in scope. Claim 9 recites that the Semliki forest virus of claim 8 is the Semliki forest virus sequence contained in plasmid pSFVI. There are no plasmid sequences involved only the virus sequences. Plasmid pSFVI is described in the prior art. The sequence generated from pSFVI is described in Example 1.
- claim 14 has been amended to replace the word "that" by "the DNA sequence"
- claim 15 has been amended to refer to "a human cytomegalovirus Intron A sequence"
- claim 16 has been amended to replace the term "nucleotide" by "DNA" in accordance with the prior claims and the term "proper" deleted. Since every DNA sequence has a 3' and 5' end, the use of the term "the 3' end" required no antecedent basis. Nevertheless, claim 16 has been amended to refer to "a 3' end".
- claim 36 has been deleted.

Having regard to the above and the amendments made to the claims, it is submitted that claims 1, 6, 8 to 10, 14 to 19 and 36 to 38, insofar as they remain in the application and in their amended form, can no longer be considered to be indefinite and hence the rejection thereof under 35 USC 112, second paragraph, should be withdrawn.

The Examiner maintained rejection of claims 1, 6, 8 to 10, 14 to 16, 18, 36 and 37 under 35 USC 102(e) as being anticipated by Parrington USP 6,060,308. The applicants maintain that there is no anticipation of the claims by the Parrington reference.

For there to be anticipation, the reference must disclose every element of the claim considered to be anticipated. Parrington does not describe a vector as

claimed in amended claim 1. While Parrington discloses a vector containing the first DNA sequence, the second DNA sequence and the promoter recited in claim 1, Parrington does not disclose such a vector containing the third sequence as recited in claim 1. In particular, while Parrington discloses a vector containing a DNA sequence which is complementary to at least part of an alphavirus RNA genome, a DNA sequence encoding RSV F or G protein or fragment and a promoter operatively connected to these DNA sequence, Parrington does not disclose, in any such vector, a third DNA sequence located between the first DNA sequence and the promoter and comprising a pair of splice sites as recited in claim 1.

The Examiner asserts in the Office Action that.

> "The CMV immediate early promoter and rabbit ß-globin intron II were used (col. 4, line 11)".

The first sentence of this statement is correct while the second is not. As previously explained, col. 4, line 11, to which the Examiner refers, is discussing the content of WO 96/40945, i.e., the Li et al reference cited by the Examiner and the vector which is described therein While the Li et al vector contains the rabbit β-globin intron II sequence, the Li et al reference does not employ a Semliki virus sequence ("first DNA sequence"). There is no disclosure in Parrington of a vector containing the β-globin intron II sequence ("third DNA sequence") in conjunction with the Semliki virus sequence.

The Parrington reference, therefore, lacks disclosure, in the same vector, of the three DNA sequences recited in claim 1.

Accordingly, it is submitted that none of claims 1, 6, 8 to 10, 14 to 16, 18, 36 and 37 are anticipated by Parrington and hence the rejection thereof under 35 USC 102(e) should be withdrawn.

The Examiner maintained rejection of claims 1, 6, 8 to 10, 14 to 16, 18, 36 and 37 under 35 USC 103 as being anticipated by Dubensky in view of Li et al.

First of all, a rejection under 35 USC 103 cannot be one of anticipation as stated by the Examiner, but one of obviousness. A rejection of anticipation must be on the basis of a single reference and not a combination of references. For the following discussion, it is assumed that the rejection in intended to be one of obviousness.

In the Office Action, the Examiner indicates that:

> "Dubensky teach an alphaviral vector encoding RSV proteins (claim 10 of '482). The alphaviral vector sequence is the "first DNA sequence" and the DNA encoding the RSV protein is the "second DNA sequence" and "third DNA sequence" as claimed. The alphavirus of Dubensky is Semliki forest virus (col. 11, line 67) which is equivalent to the sequence contain in plasmid pSFVI (claim 9)."

It is not seen how the DNA encoding the RSV protein can be considered to be the "third DNA sequence" recited in claim 1, as well as being the "second DNA sequence". They are discrete sequences as recited in claim 1, otherwise there would be no need to recite them separately. Claim 1 defines the second and third sequences as comprising different elements.

In addition, claim 1 recites that the third DNA sequence is located between the promoter and the second DNA sequence and that the third sequence comprises a pair of splice sites to prevent aberrant mRNA splicing.

Claim 1 recites that the third DNA sequence comprises a pair of splice sites which have the function of preventing aberrant mRNA splicing *in vivo*. Thus, the third DNA sequence recited in claim 1 has specific structure and function. There is no such element described in Dubensky. Despite the Examiner's urging to the contrary, there is no structure described in Dubensky which has the same structure and function as applicants third DNA sequence.

In this respect the Examiner states in the Office Action.

> "The limitation of the third DNA that comprises a pair of splice sites that prevent aberrant splicing is equivalent to the DNA sequence adjacent to the alphavirus sequence and the DNA sequence between the alphavirus sequence and the promoter taught by Dubensky. Such a sequence comprises a "pair of splice sites" because the sequence can be spliced at any two sites."

There is no such structure described in Dubensky et al. The Dubensky reference clearly lacks any teaching of a third DNA sequence which comprises a pair of splice sites.

As the Examiner indicates, Dubensky does not teach the nucleic acid sequence of RSV F or G proteins. The Examiner relies on Li et al to make up this deficiency. Whether or not, having regard to the Li et al disclosure, it would have been obvious to one of ordinary skill in the art at the time the invention was made to

use the expression vector encoding RSV protein taught by Dubensky to deliver the F and G proteins taught by Li, is immaterial, since neither reference discloses any DNA sequence which corresponds to applicants third DNA sequence having the structure and function recited in claim 1.

As discussed above, the Li et al reference discloses a CMV promoter and a rabbit β-globin intron II sequence in a DNA construct. However, also as discussed above, neither of these elements is suggested for incorporation into a Semliki virus or other alphavirus vector.

Accordingly, it is submitted that claims 1, 6, 8 to 10, 14 to 16, 18, 36 and 37, insofar as they remain in the application and in their amended form, are patentable over the cited combination of prior art and hence the rejection thereof under 35 USC 103, should be withdrawn.

It is noted that claims 19 and 38 were not included in either prior art rejection. These claims are directed to a specific nucleic acid sequence for the vector of claim 1. Having regard thereto, there would appear to be no logical reason for including claims 18 and 37 (now deleted) in the rejection, since such claims are directed to the specific plasmid, pMP44.

The Examiner maintained rejection of claims 1, 6 to 16, 18, 36 and 37 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 to 3, 5, 6, 8 and 18 to 21 of USP 6,060,308.

The relationship of the claims of this application as amended to U.S Patent No. 6,060,308 has been discussed above with respect to the rejection based upon this reference under 35 USC 102(e). It is submitted, from that discussion, that the claims of this application are patentably distinct from the claims of U.S. Patent 6,060,308.

In the Office Action, the Examiner refers to the pMP37 vector, which is provided in USP 6,060,308. Elements from this vector are used in the assembly of pMP44. However, pMP44 contains structural elements additional to those contained in pMP37. It is not true to say, as the Examiner asserts in the Final Action, that:

> "... the vectors of claims 1 to 3, 6, 8 and 18 to 21 of US Patent No. 6,060,308 are vectors as claimed in the instant application"

since the vectors of the present application contain additional elements.

Accordingly, it is submitted that claims 1, 6 to 16, 18, 36 and 37 do not represent an obviousness-type double patenting of claims 1 to 3, 5, 6, 8 and 18 to 21 of Parrington USP 6,060,308.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

It is believed that this application is now in condition for allowance and early and favourable consideration and allowance are respectfully solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Disclosure:

Please replace the paragraph beginning at page 20, line 10, with the following rewritten paragraph:

pMP42	203461	November 12, 1998

In the Claims:

Please cancel claims 36 to 38.

Claims 1, 14, 15 and 16 have been amended as follows:

1. (Thrice Amended) A vector, comprising:

a first DNA sequence which is wholly complementary to at least part of an alphavirus RNA genome, said first DNA sequence [and] having the complement of complete alphavirus RNA genome replication regions that permits *in vivo* replication;

a second DNA sequence encoding a respiratory syncytial virus (RSV) protein selected from the group consisting of the F and G glycoprotein of RSV or encoding a protein fragment which is [that induces production of antibodies that specifically react with the RSV protein, said protein fragment being] a truncated RSV F or RSV G protein lacking the transmembrane anchor and cytoplasmic tail, said second sequence being inserted into a region of the first DNA sequence which is non-essential for replication [downstream of said first sequence]; and

a third DNA sequence operatively linked to the first DNA sequence, [said third DNA sequence enhancing the immunoprotective ability of the RSV protein or fragment thereof when expression occurs *in vivo*,] said first, second and third DNA sequences being under transcriptional control of a single promoter, said third DNA sequence being located between said first DNA sequence and the promoter, [sequence] said third DNA sequence [and] comprising a pair of splice sites that prevent aberrant mRNA splicing *in vivo*.

14. (Twice Amended) The vector of claim 1 wherein said third DNA sequence is the DNA sequence [that] of rabbit β-globin intron II.

15. (Thrice Amended) The vector of claim 1 wherein said promoter sequence is an immediate early cytomegalovirus (CMV) promoter and a [the] human cytomegalovirus Intron A sequence is provided downstream of the promoter and upstream of the third DNA sequence.

16. (Twice Amended) The vector of claim 15 further comprising a fourth DNA [nucleotide] sequence at a [the] 3'-end of the first DNA [nucleotide] sequence that ensures [proper] *in vivo* cleavage at the 3'-end of the first DNA [nucleotide] sequence.